Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
January 30, 2009

Hilton Washington DC North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland

Summary Minutes

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the January 30, 2009, Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of **the Food and Drug Administration were approved on __February 19, 2010.**

I certify that I attended the January 30, 2009 meeting of the Anesthetic and Life Support Drugs Advisory Committee Meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Kalyani Bhatt
Designated Federal Official, ALSDAC

_____/s/_____
John T. Farrar, MD, PhD,
Chair

Final Summary Minutes.
Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
January 30, 2009

A verbatim transcript will be available in approximately four to six weeks, sent to the Division and posted on the FDA website at:
http://www.fda.gov/ohrms/dockets/ac/cder08.html#AnestheticLifeSupport

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Prior to the meeting, the members and the invited consultants were provided the background material from the FDA and sponsor. The meeting was called to order by John T. Farrar, M.D. (Chair, ALSDAC); the conflict of interest statement was read into the record by Kalyani Bhatt (Designated Federal Official). There were approximately 200 persons in attendance. There was 1 speaker for the Open Public Hearing Session

Attendance:

Anesthetic and Life Support Drugs Advisory Committee Members Present (voting)
John T. Farrar, MD, Jeffrey R. Kirsch, MD, Nancy Nussmeier, MD, Osemowota Omoigui, MD (Consumer Representative), Donald Prough, MD, Daniel Zelterman, PhD

Drug Safety and Risk Management Advisory Committee Members Present (voting)
Timothy Lesar, PharmD, Sean Hennessy, PharmD, PhD, Judith Kramer, MD, MS

Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Consultants (Temporary voting):
Warren Bickel, PhD, Patrick Beardsley, PhD, Sorin Brull, MD, Domenic Ciraulo, MD, Stephanie Crawford, PhD, Ruth Day, PhD, James Eisenach, MD, Jacqueline Gardner, PhD, Merrill Goozner (Acting Consumer Representative for DSaRM) William Hiatt, MD, Arthur Levin, MPH, Michael Lincoff, MD, Karl Lorenz, MD, MS, HS, Jane C. Maxwell, PhD, Lewis Nelson, MD, Jack Rosenberg, MD, Mary Tinetti, MD, James Woods, Julie Zito, PhD, Rebecca Zavacky (Patient Representative)

Industry Representative for Anesthetic Life Support Drugs (non-voting):
Bartholomew Tortella, MD, MTS, MBA

Industry Representative for Drug Safety Risk Management (non-voting):
D. Bruce Burlington, MD

Anesthetic and Life Support Drugs Advisory Committee Members Absent:
Kanwaljeet Anand, J.J. M.D., Ph.D., Jayant Deshpande, M.D.,
David G. Nichols, MD, MBA, Athena F. Zuppa, Julia Pollock, MD

Drug Safety and Risk Management Advisory Committee Members Absent:
Terry C. Davis, PhD., Sander Greenland, Dr.P.H., Susan Heckbert, MD, PhD
Open Public Speakers:

Cynthia Reilly, BS, PharmD
Director, Practice Development Division, American Society of Health-System Pharmacists

AGENDA

The committees will discuss the safety and efficacy of propoxyphene and propoxyphene-combination products for the treatment of mild to moderate acute pain.

Call to Order Introduction of Committee	**John T. Farrar, M.D.** Chair, ALSDAC
Conflict of Interest Statement	**Kalyani Bhatt** Designated Federal Officer, ALSDAC/DSaRM
Opening Remarks	**Sharon H. Hertz, M.D.** Deputy Director Division of Anesthesia, Analgesia, & Rheumatology Products, CDER/FDA
Public Citizen Presentation	**Sidney Wolf, M.D.** Public Citizen
Sponsor Presentations **Pharmaceuticals**	**Xanodyne Pharmaceuticals** **Qualitest/Vintage**
Development & Research	**James B. Jones, M.D., PharmD,** Vice President, Clinical Medical Affairs Xanodyne Pharmaceuticals, Inc.

Jody L. Green, Ph.D.
Denver Health/Rocky Mountain
Poison & Drug Center,
Associate Research Director
Vanderbilt University,
Assistant Professor, Denver Co

Lauren Shaiova, M.D.
Chief of Department of Pain & Medicine & Palliative Care, Metropolitan Hospital Center
Division of Health and Hospital Corporation, New York, NY

Regulatory History and Clinical Efficacy of Propoxyphene Products

Analgesia, &
Products, CDER/FDA

Jin Chen, M.D.
Medical Officer
Division of Anesthesia, Rheumatology

Clinical Pharmacology of Propoxyphene

Sheetal Agarwal, Ph.D.
Clinical Pharmacologist Reviewer
Office of Clinical Pharmacology
CDER/FDA

Non-Clinical Toxicology Findings

Steve Leshin, Ph.D.
Pharmacology/Toxicology Reviewer
Division of Anesthesia, Analgesia, & Rheumatology Products,
CDER/FDA

Utilization Trends for Propoxyphene Products

Hina Mehta, PharmD.
Drug Utilization Analyst
Office of Surveillance and Epidemiology
CDER/FDA

Findings from AERS Analysis and Epidemiological Review of Cardiotoxicities Associated with Propoxyphene	**Joann Lee, PharmD.** Office of Surveillance and Epidemiology, CDER/FDA
Misuse/Abuse of Propoxyphene Products: Findings from The Drug Abuse Warning Network (DAWN)	**CAPT Kathy Poneleit** United States Public Health Service Director, Division Facility Survey Office of Applied Studies, SAMHSA

Open Public Hearing

Questions to the presenters

Discussion and Questions to the Committee

Adjourn

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

QUESTIONS TO THE COMMITTEE

January 30, 2009

The committees will discuss the safety and efficacy of propoxyphene and propoxyphene-combination products for the treatment of mild to moderate acute pain.

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1. Based on the data that have been presented regarding the efficacy of propoxyphene-containing products:

    a. Discuss whether you agree or disagree that there is evidence of efficacy for propoxyphene as monotherapy.

    The committee stated that the evidence of efficacy for propoxyphene as monotherapy was marginally better than placebo and never greater than acetaminophen, and that the data was of insufficiently quality to be conclusive. This is a subtle but potentially important difference.

    b. Discuss whether you agree or disagree that there is evidence that propoxyphene contributes to the efficacy of propoxyphene and acetaminophen combination products.

    The evidence presented suggested that propoxyphene with acetaminophen was marginally better than acetaminophen alone, in a few studies and no-different in a few studies. A trend towards a small difference was seen in the meta –analysis but was not statistically significant. The available data was of insufficient quality to be conclusive.

2. Based on the data that have been presented regarding the nonclinical cardiac effects of propoxyphene and the postmarketing reports of deaths in which propoxyphene was identified,

    a. Discuss whether there is evidence that propoxyphene is cardiotoxic in the therapeutic range.

    General consensus from the committee members was that there was no evidence for clinically relevant cardiotoxicity in the current therapeutic dose range. No data was presented that supported a rate of death per prescription that was higher than any of the potential comparator analgesics.

b. Discuss whether additional data are needed to adequately assess the potential for cardiac effects, and if so, what data.

The committee recommended further studies of rate and clinical relevance of QT prolongation at usual therapeutics doses, at high systemic exposures, and with multiple drug exposure. Specific studies of the overall risk of the use of the drug are needed in the elderly, including but not limited to QT prolongation.

3. Propoxyphene-containing products are the second most frequently prescribed opioid analgesic in the U.S. Discuss the potential risks associated with the replacement of propoxyphene-containing products by the alternative products listed below should propoxyphene-containing products be removed from the market.

   Propoxyphene-containing products are listed under Schedule IV of the Controlled Substances Act. Alternatives to propoxyphene-containing products include NSAIDs, tramadol (unscheduled), butorphanol (Schedule IV), codeine/ acetaminophen combination products (Schedule IV), and hydrocodone/ acetaminophen combination products (Schedule III).

   The general consensus of the committee was that the drug may not have much more effect than placebo, but that the risk from therapy is quite small. The action of taking the drug off the market will likely result in an uncomfortable situation for the pain provider, since the most appropriate choice for replacement would be acetaminophen alone. The effect on patient care of taking the drug off the market would depend on what medication that providers chose to use instead. It seems likely that providers may prescribe a drug that would have a higher risk profile than propoxyphene in a significant number of cases. The alternative substitute medications listed are all considered more efficacious, but carry similar or great risks. All of the alternatives are likely to be at least equally problematic for the elderly.

4. Based on the data presented, does the balance of risk and benefit support continued marketing of propoxyphene-containing products for the management of mild to moderate pain? *(vote)*

   Yes: 12
   Tinetti, Lorenz, Rosenberg, Brull, Prough, Nussmeier, Farrar, Crawford, Zavacky, Maxwell, Kramer, Lincoff

   No: 14
   Beardsley, Osemwota, Eisenach, Zito, Woods, Hennessey, Lesar, Gardner, Goozner, Nelson, Day, Levin, Hiatt , Zelterman

Abstain: 0

<u>Members that left the meeting before voting:</u> Ciraulo, Kirsch, Bickel

a. If you conclude that the balance of risk and benefit is unfavorable and these products should no longer be marketed, could additional information about safety or efficacy change your conclusion?

   The committee recommended a conclusive high quality study of efficacy and additional data about the risks of propoxyphene and the alternative analgesics would be needed.

b. If you conclude that the balance of risk and benefit is favorable enough to support continued marketing, are there changes that should be made to the labeling?

   The committee recommended efforts to change the use of propoxyphene products in clinical practice, especially in the elderly, by revising the labeling and educating health care providers.

The meeting adjourned at 4:00 PM.

_____/s/_____ ____/s/_____

John T. Farrar, MD, PhD, Chair Kalyani Bhatt, DFO